

Is the Freeman-Tukey double arcsine transformation a reliable approach for proportion meta-analysis ?

An example with a Living SR on Covid-19 vaccines and Pregnancy outcomes.

Ciapponi A, Bardach A, Glujovsky D, Berrueta M, Castellana N

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abardach@iecs.org.ar @Ariel_Bardach

Institute for Clinical Effectiveness and Health Policy



No conflicts of interest

Previous work

Recently questioned...

- Meta-analysis often utilizes pooling of proportions to gain more accurate estimates of disease frequency, such as cumulative incidence or prevalence. They are usually based on transformed proportions using Freeman-Tukey double arcsine transformations (FTT).
- A recent study proposed the use of generalized linear mixed models (GLMM) over FTT, on the premise the latter produces misleading results, sparking controversy.[1]
- However, other authors, using the same set of studies, reanalyzed the data and concluded that the FTT is the most reliable approach and remains the preferred transformation in proportion meta-analysis.[2]
- We aimed to compare the performance of FTT with GLMM in a large set of proportion meta-analyses from an ongoing Living Systematic Review.

1. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods*. 2019;10: 476–483.

2. Doi SA, Xu C. The Freeman-Tukey double arcsine transformation for the meta-analysis of proportions: Recent criticisms were seriously misleading. *J Evid Based Med*. 2021;14: 259–261.

COVID-19 Vaccines for Pregnant A Living Systematic Review and

Last update was made on 9/3/2023

This is a regularly updated, comprehensive database and synthesis of published literature relating to COVID-19 vaccines in pregnancy. To start your search, click on any given country on the map to see all collected studies or click on the Outcomes tab for details on studies reporting on Maternal Pregnancy Outcomes, Maternal Adverse Events Following Immunization, Infant Safety Outcomes, Vaccine Efficacy/Effectiveness Outcomes, and Immunogenicity. For more information on the Living Systematic Review (LSR) and inclusion criteria, click the Methodology and About tabs.

Filters applied: None

- ALL STUDIES
- OUTCOMES
- METHODOLOGY
- SUMMARY TABLES
- META-ANALYSIS
- Filters
 - PUBLICATION DATE
 - COUNTRY/LOCATION

162 Collected Studies 597,291 Vaccinated Population 12 Published in the Last 6 Months 37 Number of Countries 11 Vaccine Products

Studies Collected per Country



Studies by Vaccine Type/Platform



Analysis parameters

Outcome type

- Efficacy/Effectiveness
- Infant safety outcomes following COVID-19 vaccination during pregnancy
- Maternal-Pregnancy related outcomes

Outcome

Stillbirth

Subgroup analysis

- Trimester
- Dominant variant
- Vaccine type
- Dose

Vaccine type

- RNA
- Viral vector

Dose

- Not specified

Dominant Variant

- Not specified

Effect measure

- RR

Type of Pregnant Population Exposed to COVID-19 vaccination

General pregnant population vaccinated

Forest Plot / Meta-analysis Summary table

We identified 37 studies reporting this outcome. Based on the methodology described, only 4 studies reported adjusted effect measures for this outcome: Dick, A (2022) (a), Fell, D.B. (2022), Hui, L (2022), Magnus, M.C. (2022). Finally, 3 were included in the meta-analysis based on the filters. The meta-analysis included a total of 84,744 patients exposed to the vaccine in 3 countries: Australia, Canada and Israel.

Maternal safety of COVID-19 vaccines during pregnancy versus unvaccinated pregnant population: Stillbirth.



COVID 19 vaccines for pregnant persons: a living systematic review and meta-analysis

<https://safeinpregnancy.org/lsr/>

Methods

- We conducted GLMM[1] and FTT over a **large dataset** of proportions **from a living systematic review** and meta-analysis about **safety, immunogenicity, and effectiveness of COVID-19 vaccines** for pregnant people (<https://safeinpregnancy.org/lsr/>) applying recommended safeguards (using corrected statistical packages: Metan in Stata) and other approaches (GLMM and Metaprop in R):

Safeguards:

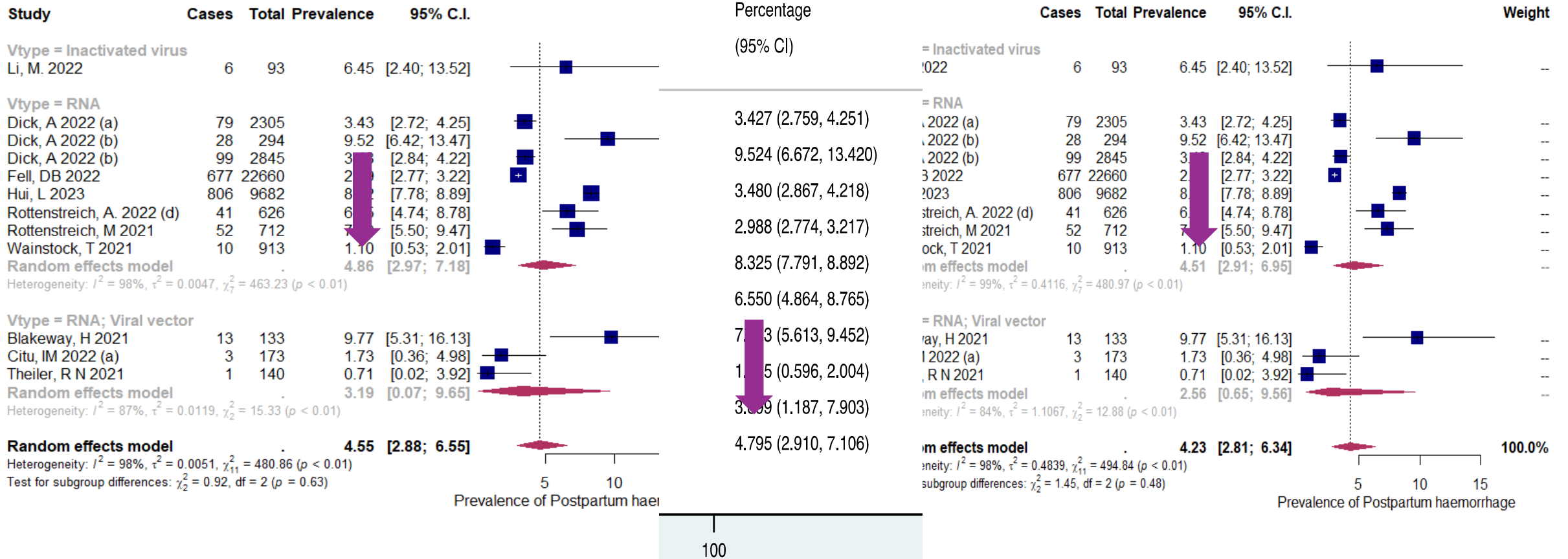
- a) avoiding the use of the average of the double arcsine and its variance for synthesis;
 - b) using the inverse of the variance of the pooled FTT proportion
 - c) modifying the confidence intervals to prevent numerical inaccuracies.
- Compared results for MAs with few/several studies, and for Vaccine outcomes/Adverse effects

Postpartum Hemorrhage

FTT (Metaprop R)

Metan (metan [corr], Stata)

GLMM



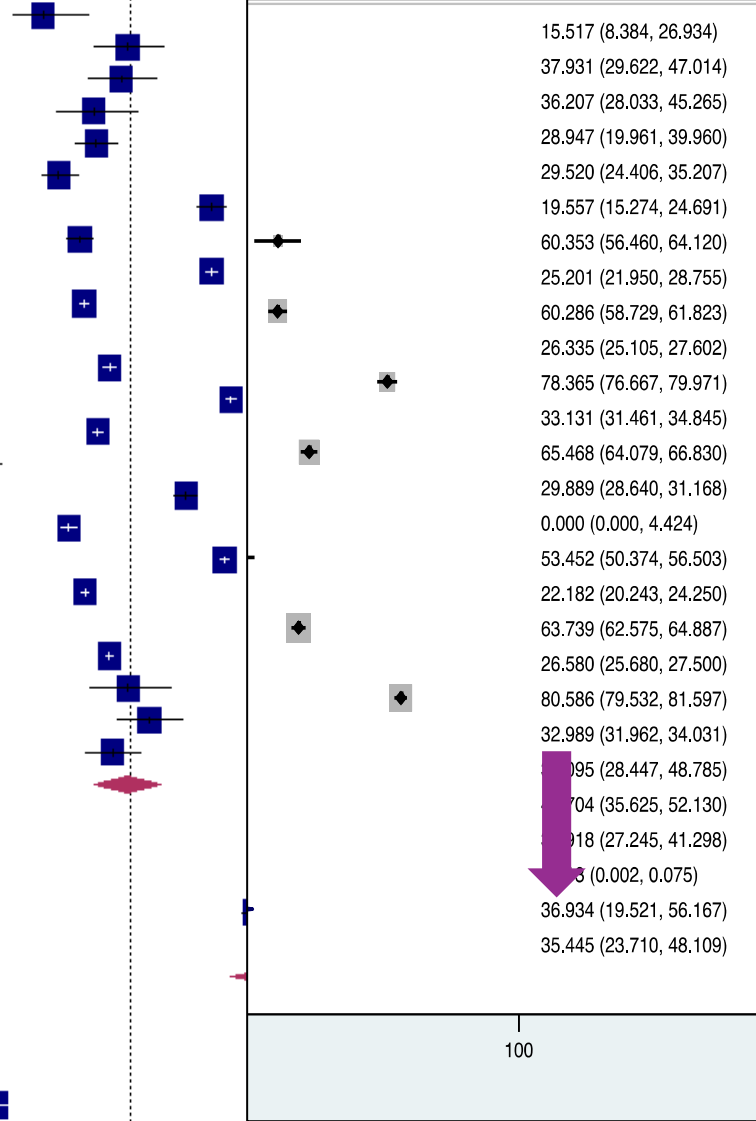
Fatigue

FTT (Metaprop R)

Metan (metan [corr], Stata)

GLMM, R

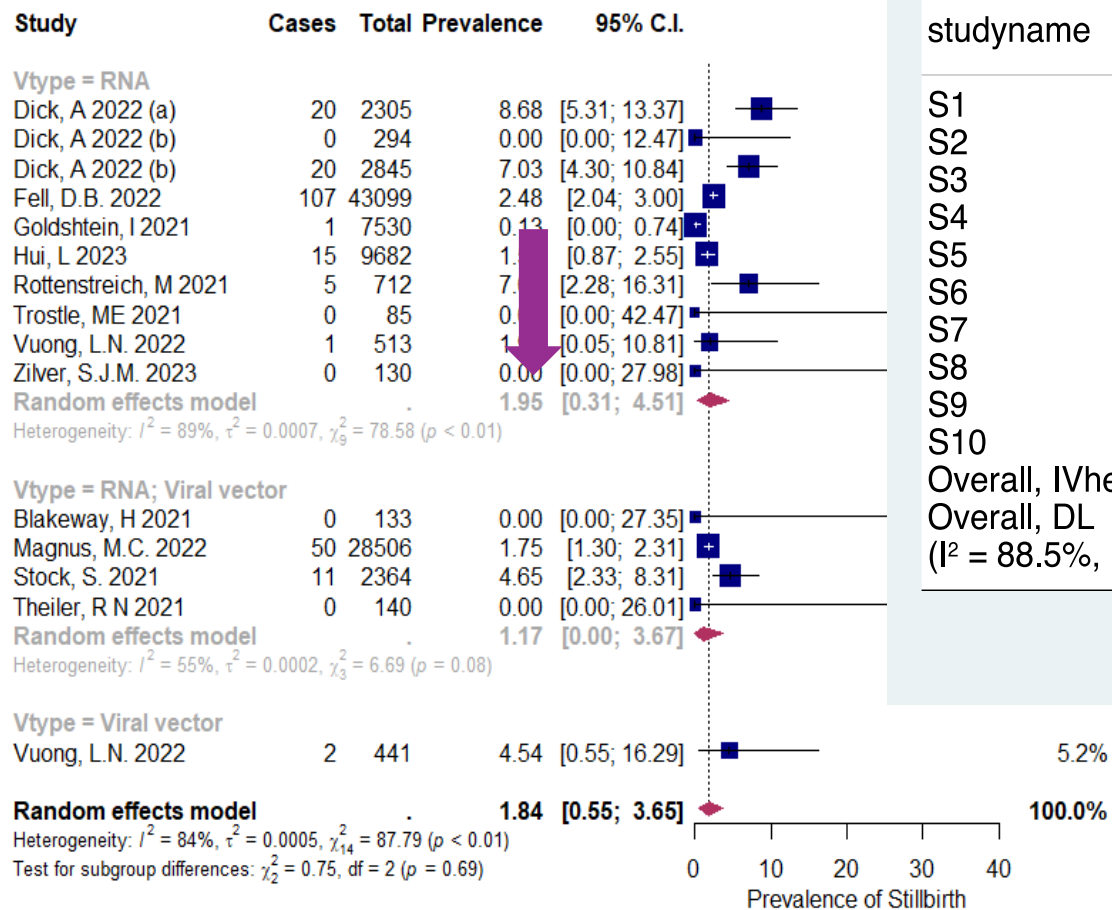
Ben-Mayor Bashi, T 2021	9	58	15.52	[7.35; 27.42]
Blakeway, H. 2022	44	116	37.93	[29.09; 47.41]
Blakeway, H. 2022	42	116	36.21	[27.49; 45.65]
Cahen-Peretz, A. 2023	22	76	28.95	[19.11; 40.49]
Favre, G. 2022	80	271	29.52	[24.16; 35.34]
Favre, G. 2022	53	271	19.56	[15.01; 24.79]
Favre, G. 2022	376	623	60.35	[56.39; 64.22]
Favre, G. 2022	157	623	25.20	[21.84; 28.80]
Kachikis, A 2021	2315	3840	60.29	[58.72; 61.84]
Kachikis, A 2021	1258	4777	26.33	[25.09; 27.61]
Kachikis, A 2021	1869	2385	78.36	[76.66; 80.00]
Kachikis, A 2021	984	2970	33.13	[31.44; 34.86]
Komine-Aizawa, S 2022	3003	4587	65.47	[64.07; 66.84]
Komine-Aizawa, S 2022	1504	5032	29.89	[28.63; 31.17]
Nakahara, A 2022	0	83	0.00	[0.00; 4.35]
Shapiro Ben David, S 2022	542	1014	53.45	[50.33; 56.56]
Shapiro Ben David, S 2022	366	1650	22.18	[20.20; 24.27]
Shimabukuro, T. T. 2021	4231	6638	63.74	[62.57; 64.90]
Shimabukuro, T. T. 2021	2406	9052	26.58	[25.67; 27.50]
Shimabukuro, T. T. 2021	4541	5635	80.50	[79.53; 81.61]
Shimabukuro, T. T. 2021	2616	7930	32.00	[31.95; 34.04]
Toussia-Cohen, S. 2022 (a)	32	84	38.00	[27.71; 49.34]
Zilver, S.J.M. 2023	59	135	43.00	[35.19; 52.50]
Zilver, S.J.M. 2023	58	171	33.00	[26.87; 41.54]
Random effects model			37.72	[29.20; 46.64]
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 0.0515$, $\chi^2_{24} = 10678.71$ ($p = 0$)				
Vtype = RNA; Viral vector				
Brinkley, E. 2022	677	946	71.56	[68.57; 74.42]
Citu, IM 2022 (a)	188	227	82.82	[77.27; 87.49]
Random effects model			77.16	[65.36; 87.12]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0082$, $\chi^2_1 = 13.06$ ($p < 0.01$)				
Vtype = Viral vector				
Gahndi, A 2022	7	247	2.83	[1.15; 5.75]



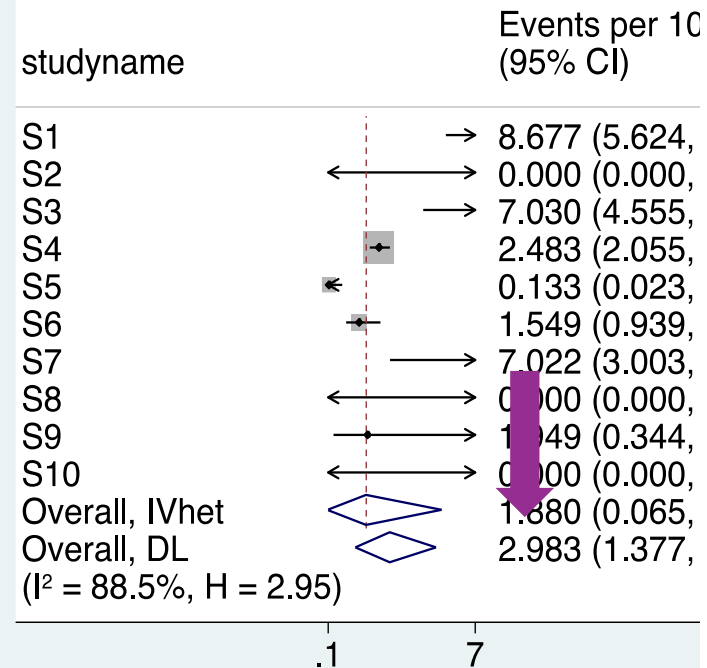
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Zilver, S.J.M. 2023	58	171	33.00	[26.87; 41.54]
Random effects model			36.70	[27.93; 46.44]
Heterogeneity: $I^2 = 100\%$, $\tau^2 = 1.0152$, $\chi^2_{24} = 8706.09$ ($p = 0$)				
Vtype = RNA; Viral vector				
Brinkley, E. 2022	677	946	71.56	[68.57; 74.42]
Citu, IM 2022 (a)	188	227	82.82	[77.27; 87.49]
Random effects model			77.09	[68.13; 84.12]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0881$, $\chi^2_1 = 11.68$ ($p < 0.01$)				
Vtype = Viral vector				
Gahndi, A 2022	7	247	2.83	[1.15; 5.75]

Stillbirth

FTT (metaprop, R)



Metan (metan [corr], Stata)



GLMM (R)

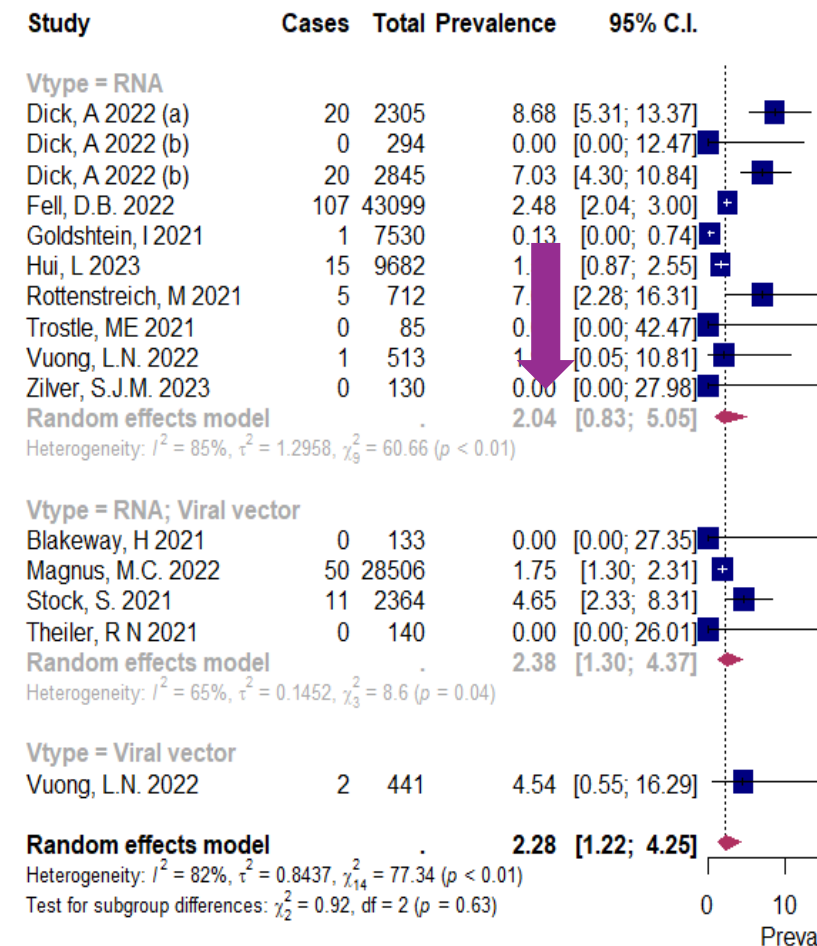


Table. Summary of MA results per vaccine type subgroup considering FTT and GLMM approaches

Outcome	Subgroup	#studies	FTT				GLMM				Rel Diff (%)	Abs Diff
			prop	Prop-95% CI	I ² %	I ² %-95% CI	prop	Prop-95% CI	I ² %	I ² %-95% CI		
PPH	Inactivated virus	1	6.450	[2.20; 12.50]	NA	NA	6.450	[2.93; 13.62]	NA	NA		
	RNA	8	4.860	[2.97; 7.18]	98.49	[97.95;98.89]	4.510	[2.91; 6.95]	98.54	[98.03;98.92]	7.20	0.350
	RNA; Viral vector	3	3.190	[0.07; 9.65]	86.95	[62.75;95.43]	2.560	[0.65; 9.56]	84.47	[53.74;94.79]	19.75	0.630
Stillbirth	RNA	10	1.945	[0.307; 4.512]	88.55	[81.03;93.09]	2.045	[0.826; 5.053]	85.16	[74.47;91.38]	5.14	0.100
	RNA; Viral vector	4	1.172	[0.001; 3.671]	55.16	[0.00;85.16]	2.380	[1.296; 4.366]	65.11	[0.00;88.15]	103.07	1.208
	Viral vector	1	4.535	[0.068; 13.620]	NA	NA	4.535	[1.135; 17.946]	NA	NA		
Fatigue	RNA	25	37.720	[29.20; 46.64]	99.78	[99.76;99.79]	36.700	[27.93; 46.44]	99.72	[99.70;99.75]	2.70	1.020
	RNA; Viral vector	2	77.160	[65.36; 87.12]	92.34	[73.92;97.75]	77.090	[68.13; 84.12]	91.44	[69.92;97.56]	0.09	0.070
	Viral vector	1	2.830	[1.07; 5.33]	NA	NA	2.830	[1.36; 5.82]	NA	NA		
Apgar score<7 at five minutes	RNA	13	1.260	[0.76; 1.88]	89.38	[83.68;93.09]	1.210	[0.76; 1.91]	80.21	[67.02;88.13]	3.97	0.050
	RNA; Viral vector	3	1.310	[1.17; 1.45]	0.00	[0.00;89.60]	1.510	[1.37; 1.65]	0.00	[0.00;89.60]	15.27	0.200
SAEs	RNA	5	0.254	[0.129; 0.407]	0.00	[0.00;79.20]	0.559	[0.424; 0.737]	0.00	[0.00;79.20]	120.07	0.305
	Viral vector	1	0.405	[0.000; 1.731]	NA	NA	0.405	[0.057; 2.816]	NA	NA		



Conclusions

- We compared methods across different type of outcomes in studies about COVID-19 vaccination in pregnant persons
- FTT continues to be the a valid method under new implementations of statistical software.
- Ensuring the optimal method for conducting meta-analyses of proportions is essential, as it plays a pivotal role in making accurate estimations in epidemiology and guiding decision-making processes.

Thank You!